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Machine Learning for Clustering Dyslipidemia Patients with Statin Intolerance in Germany

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Background

- European Atherosclerosis Society and European Society of Cardiology recommend reducing low-density lipoprotein cholesterol (LDL-C) to manage dyslipidemia[1]
- Although statin therapies are the mainstay drugs for reducing LDL-C, up to 15% of patients experience statin intolerance (SI), manifested by poorly defined clinical symptoms[2]
- Our understanding of SI and the SI patient characteristics remains incomplete
- Unsupervised machine-learning techniques such as clustering can be deployed to identify patient subgroups with common features and help identify hidden patterns, enabling a better understanding of the condition

Objective

This study aimed to characterise clusters of similar SI patients based on diagnosis codes, and understand distinct comorbidities, CV risk, lipid-lowering therapy (LLT) usage exhibited in clusters

SI identification Methodology

1. This retrospective cohort study used outpatient data from a high – dimensional Electronic medical record dataset in Germany (IQVIA™ Disease Analyzer)
2. The study included 292,603 patients aged >18 years with high cardiovascular (CV) risk, atherosclerotic cardiovascular disease (ASCVD) and/or hypercholesterolemia and those on lipid-lowering therapies (LLTs) between 2017 and 2020
3. Criteria listed in Table 1, were used to identify patients with high confidence SI (n=12,869). The definitions were identified using expert and literature-informed[3] rules

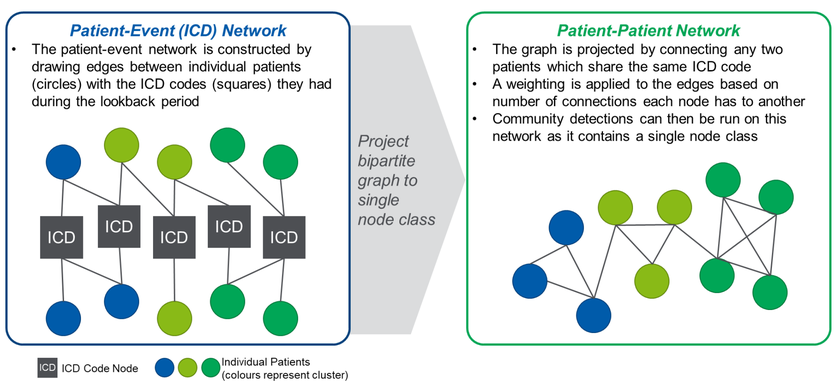
Table 1: Rules to Identify SI Patients With High Confidence[4]

- Patients with ASCVD and high CV risk only on non-statins, (OR)
- Patients with a history of long-term discontinuation of statins (>180 days) AND with events of statin down-titration, low-dose statin use, multi-statin use, statin-associated muscle symptoms (SAMS), intermittent dosing, documented SI in notes or prior discontinuation

Clustering Methodology

4. Clustering was performed on high-confidence SI patients
5. Patients were linked via common diagnosis codes to build a graphical representation (Figure 1)
6. To identify communities of patients the patient-event graphs were projected to a patient-patient graphs (Figure 1)

Figure 1: Patient-event and patient-patient network



7. Community detection approach was used to find patient clusters. Each node represents a patient while each edge represents a relationship (based on diagnoses)
8. The clusters were based on ICD* codes as events, while LLT and SI events were measured as outcomes
9. Based on performance metrics and the type, size and number of clusters produced, the Greedy modularity maximization,[5] a community detection algorithm, was applied to the patient-patient graph
10. Graph-based clustering approach was used to handle high-dimensional sparse patient data

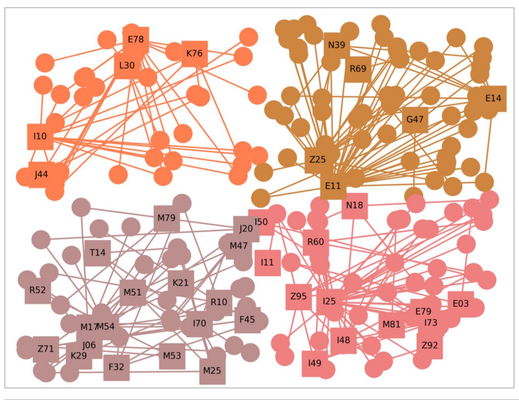


Figure 2: Representative graph of Clusters obtained in Males Aged ≥60 years

Results

- The clustering algorithms were applied to 4 (disjoint) subsets of patients based on gender (male/female) and age (≥60 years and <60 years)
- Across the subsets, 8 key clinically meaningful clusters were identified. See Figure 2 as an illustrative example of identified cluster

Male patients ≥60 years of age

Three key clinically meaningful clusters identified
Total patients in group: 1,988

1. **Patients with predominant musculoskeletal Disorders, n=419 (21.1%)**
2. **Patients with somatoform disorders, along with gastric and musculoskeletal disorders and symptoms, n=367 (18.5%)**
3. **Patients with CKD*, on chemotherapy and other cardiac conditions (hypertensive heart disease and arrhythmias), n=327 (16.4%)**

Dominant cluster: 1

Mean age	Male patients ≥60 years of age	n=419 (21.1%)
75.0		

Comorbidities

Joint diseases	(36.3%)
Gonarthrosis	(31.0%)
Soft tissue diseases	(31.7%)
Spondylosis	(13.6%)
Gout	(12.2%)

Key SI event

SAMS	(15.8%)

CV risk

ASCVD	(64.2%)

Past statin therapy

Simvastatin	48.4%
Atorvastatin	38.7%
Pravastatin	6.4%

Ezetimibe use

Ezetimibe FDC*	Ezetimibe mono
7.6%	15.5%

Female patients ≥60 years of age

Two key clinically meaningful clusters identified
Total patients in group: 1,478

1. **Patients with musculoskeletal disorders including osteoporosis, anxiety and obesity, n=417 (28.2%)**
2. **Patients with obesity, CKD* and hypertensive heart disease, n=326 (22.1%)**

Dominant cluster: 1

Mean age	Female patients ≥60 years of age	n=417 (28.2%)
77.6		

Comorbidities

Osteoporosis	(18.2%)
Diseases of spine and neck	(18.0%)
Obesity	(15.8%)
Anxiety	(15.1%)

Key SI event

SAMS	(18.2%)

CV risk

ASCVD	(51.6%)

Past statin therapy

Simvastatin	47.5%
Atorvastatin	44.1%
Pravastatin	9.6%

Ezetimibe use

Ezetimibe FDC*	Ezetimibe mono
4.6%	17.3%

SI patients - key clusters

Male patients <60 years of age

Two key clinically meaningful clusters identified
Total patients in group: 1,117

1. **Patients with diabetes, hypertensive heart disease and metabolic/endocrine disorders, n=307 (25.6%)**
2. **Patients with depression, somatoform disorders, along with a variety of musculoskeletal, gastric symptoms, and related conditions, n=558 (46.6%)**

Dominant cluster: 2

Mean age	Male patients <60 years of age	n=558 (46.6%)
52.6		

Comorbidities

Soft tissue diseases	(33.3%)
Depression	(28.0%)
Gastritis and duodenitis	(25.8%)
Other GI* disease	(22.0%)
Joint disorders	(22.6%)
Somatoform disorders	(20.8%)

Key SI event

SAMS	(21.0%)

CV risk

ASCVD	(43.4%)

Past statin therapy

Atorvastatin	52.2%
Simvastatin	44.3%
Pravastatin	6.1%

Ezetimibe use

Ezetimibe FDC*	Ezetimibe mono
8.1%	14.0%

Female patients <60 years of age

One key clinically meaningful cluster identified
Total patients in group: 663

1. **Patients with predominant depressive episodes, along with a variety of musculoskeletal, mental, behavioral, and metabolic disorders, n=314 (47.4%)**

Dominant cluster: 1

Mean age	Female patients <60 years of age	n=314 (47.4%)
53.5		

Comorbidities

Depression	(45.5%)
Soft tissue disease	(36.9%)
Gastritis and duodenitis	(23.9%)
Joint diseases	(22.6%)
Somatoform disorders	(22.0%)
Obesity	(20.7%)

Key SI event

SAMS	(21.3%)

CV risk

ASCVD	(42.4%)

Past statin therapy

Atorvastatin	51.3%
Simvastatin	48.7%
Pravastatin	7.0%

Ezetimibe use

Ezetimibe FDC*	Ezetimibe mono
6.1%	14.0%

Key Messages

1. Clusters of SI patients in <60 years age group are larger, though much more diffuse in terms of diagnoses observed within the cluster than those of ≥60 years of age group
2. The key SI event in clusters with dominant musculoskeletal, depression, anxiety and somatoform disorders is SAMS
3. Depression, anxiety and somatoform disorders are important associated co-morbidities driving dominant and clinically meaningful clusters across age and gender groups
4. Ezetimibe monotherapy use is more common in clusters of patients ≥60 years of age

Conclusions

Unsupervised clustering technique generated distinct personas of SI patients by age and gender in Germany. The study provides insights on distinct patient clusters, which can be leveraged to inform diagnosis and optimal treatment pathways for SI patients

References:

1. European Heart Journal 2019;41:111-188; doi: 10.1093/eurheartj/ehz455
2. Circulation. 2015;131:e389–e391; doi: 10.1161/CIRCULATIONAHA.114.013189
3. Value in Health 2016;19:852-860; doi: 10.1016/j.jval.2016.03.1858
4. Clinical Therapeutics 2021;43:1583-1600; doi: 10.1016/j.clinthera.2021.07.019
5. Journal of Engineering & Technology 2018;7:857-863; doi: 10.14419/ijet.v7i4.19.28058

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* FDC: Fixed-dose combination; ICD, International classification of diseases; CKD, chronic kidney disease; GI, Gastrointestinal disease